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EXPERIMENTAL PHYSIOLOGICAL AND HISTOCHEMICAL STUDY
OF THE ADAPTATION OF INTESTINAL TRANSPLANTS
INCORPORATED IN THE URINARY SYSTEM

by S. Z. Fridkin

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EXPERIMENTAL PHYSIOLOGICAL AND HISTOCHEMICAL STUDY
OF THE ADAPTATION OF INTESTINAL TRANSPLANTS
INCORPORATED IN THE URINARY SYSTEM

- USSR -

[Following is a translation of an article by S. Z. Fradkin, Novokuznets State Institute for the Advanced Training of Physicians, and Institute of Experimental Biology and Medicine, Siberian Department of the Academy of Sciences USSR, Novosibirsk, in the Russian-language periodical Izvestiya Sibirskogo Otdeleniya Akademii Nauk SSSR (News of the Siberian Department of the Academy of Sciences USSR), No 8, Novosibirsk, 1962, pages 103-109. The article was submitted to the editor 2 December 1961.]

A large number of works are devoted to intestinal plastic surgery of the urinary bladder. However, the mechanism of adaptation of the transplant and the bladder is not completely clear. Up to this time, there have been differences of opinion concerning the use of small or large intestine for plastic surgery of the urinary bladder. Therefore, the given problem remains an urgent one for contemporary urology.

The literature contains contradictory morphological data on intestinal plastic surgery [1-6, etc.]. In the light of contemporary morphology, these works cannot be considered complete, since the histological methodology used by different

authors in studying morphological changes does not afford the possibility of studying localization of any biochemical processes in tissue microstructures in different functional conditions. As is known, the methods of histochemical investigation make it possible to explain the nature of such processes. We found no work in the literature devoted to a histochemical study of the problem. Attempting to fill the existing gap to some extent and considering the significance of mucopolysaccharides in tissue adaptation and processes of healing, we used a number of physiological, histological, and histochemical methods to acquire an answer to two problems of practical importance: 1) what is the nature of the processes of connection and adaptation of tissues of the urinary bladder and the intestine? and 2) what are the characteristics of these processes in case of ileo- and sigmoidocystoplasty?

MATERIAL AND METHODS

Operations were performed on 40 dogs. Subtotal resection of the urinary bladder with subsequent sigmoidocystoplasty (with a closed section) or J-form ileocystoplasty was performed.

Cystometric investigation was carried out in 15 dogs before operation and in 17 dogs at different periods after plastic surgery. A water cystomanometer with a recording apparatus was used. Preparations of the urine reservoirs of 24 dogs were studied with the aid of histochemical and histological methods. The preparations were collected at the following times: 1, 4, 11, 20 days, and 1, 1½, 3, 4, 6,

and 12 months after operation. Pieces of a normal urinary bladder and of iliac and sigmoid intestine taken from three dogs were also examined. Hematoxylin-eosin stain according to van Gieson, azan according to Heidenhain, and impregnation according to Gemer were used. Mucopolysaccharides were investigated with the aid of: 1) the SHIK reaction; 2) staining with Alcian blue; 3) complement fixation of colloidal iron hydroxide according to Hale; 4) the reaction of metachromase with toluidine blue (at different pH values); 5) staining with Alcian blue with a subsequent SHIK reaction, and also according to Ritter-Olison.

Histochemical differential analysis of mucopolysaccharides was carried out according to a regimen suggested by V. V. Vinogradov and B. B. Fuks [7].

RESULTS OF THE INVESTIGATION AND THEIR EVALUATION

Cystometric investigation permitted us to establish that the inclusion of transplants as an active component part of the urinary bladder occurs gradually. With the passage of time after the operation, the functional indexes of the vesica urinaria gradually approached normal.

The different cystometric indexes of the vesica urinaria after ileo- and sigmoidocystoplasty were conditioned by the different effect of the intestinal transplants. In the case of sigmoidocystoplasty, normalization of these indexes occurs over a shorter period (Figure 1).

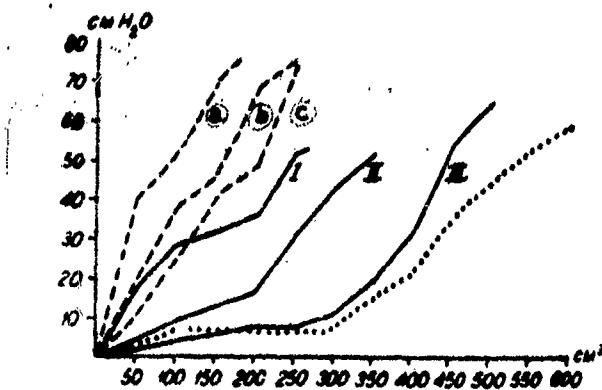


Figure 1. Cystometrograms of dogs at different periods after operation.

Legend:

- Cystometrogram of a dog before operation
- - - Cystometrogram of the dog Fal'ma
- a - after one month
- b - after 6 months
- c - 9 months after ileoplasty
- Cystometrogram of the dog Kirobochka
- I - after one month
- II - after 6 months
- III - 9 months after sigmoidocystoplasty.

It was established with the aid of histological methods that there are fractions of neutral and acid mucopolysaccharides in the goblet cells, in the cuticle, and in the contents of the crypts of normal small and large intestine; the mucopolysaccharides contain strongly dissociated acid groups not comparable to the sulfate group of the sulfomucopolysaccharides.

Glyco- and mucoproteins, hyaluronic acid, and some glycogen are contained in the stroma of the mucosa. Granules of SHIK-positive material in the tunica muscularis were identified with glycogen. These data correspond with the data of Mueller [8], Burk [9], etc. Neutral mucopolysaccharides are contained in all the goblet cells, and acid, only in the larger. Such cells are localized principally in the surface and middle sections of the mucosa. Evidently, neutral ones can be used for the formation of acid mucopolysaccharides, and the relationship of the quantities of both fractions is connected with a definite functional condition of the goblet cells. The significance of the acid mucopolysaccharides is not explained by the fact that they are "cluing" and "lubricating" material. As is known, they play an active role in the process of the interaction of the animal organism with infection agents, in tissue permeability, in the control of enzymatic processes, etc. [(10, 11), etc.]. Actually, biological defense properties of the mucus are also conditioned by these varied properties. Mueller [8] established that the substantia, which binds colloidal iron, affects absorption by the intestinal mucosa. Thus, it can be assumed that with a change in the quality and quantity of the mucopolysaccharides in the mucus, its defensive properties are also changed.

A large amount of glycogen, localized in the supporting

cells and in the cells of the middle part of the epithelial layer, is observed in the transitional epithelium of the normal urinary bladder. Glyco- and mucoproteins and also hyaluronic acid are contained here. There are glyco- and mucoproteins and chondroitin sulfate C in the stroma of the mucosae, in the submucosal layer of the intermuscular connective sheets, and in the tunica serosa. A large amount of glycogen is observed in the muscle layer of the bladder.

K. Goldi [12], A. Ya. Fridenshteyn [13], etc., indicated a high content of glycogen in transitional epithelium. In the opinion of K. Goldi [12], a substance close to hyaluronic acid--urine mucoid--is formed from glycogen in transitional epithelium. In the surface layers of the epithelium, this substance is transformed into a substantia which protects the mucous membrane from the action of urine and which is difficultly soluble in water.

After intestinal plastic surgery of the urinary bladder, the course of certain histophysiological processes in the tissues of the transplants and in the bladder stump is altered. At an even earlier period after the operation, the amount and size of the goblet cells are increased in the mucous membrane of both transplants together with degeneration and sloughing of intestinal epithelium.

Reinforcement of processes of mucus formation after intestinal plastic surgery is well known. The mucus film formed at the surface of the small intestine segment is regarded as a physico-chemical biological membrane which

protects the mucous membrane and reduces the possibility of absorption of urine products ([16], etc.).

In our experiments, the formation of such a membrane was observed toward the 11th-20th day after both types of plastic surgery. The quantity of mucopolysaccharides in the secretions of the goblet cells is decreased and their quality is altered. Primarily acid mucopolysaccharides are accumulated (Figures 2 and 3). Consequently, not only an increase in the production of mucus and the formation of mucous membrane, but also a change in the qualitative content of the mucus, which is manifested by a prevalence of acid mucopolysaccharides, plays a part in the adaptation of mucous membrane to the transplant. This supposition is substantiated by data obtained later when the amount of mucus was decreased, and the predominance of acid mucopolysaccharides in it was maintained.

The above-described adaptive changes in processes of mucus formation were more pronounced in the mucosa of the large intestine segment; here the mucosa was more compact. Together with the slight phenomena of degeneration and sloughing of intestinal epithelium, this makes it possible to note the great sensitivity of the mucosa of the small intestine to the action of urine, to which fact Gaza [2] and Scheele [14] also devoted attention.

The change in the localization and accumulation of glycogen in the transitional epithelium (Figure 4) is



Figure 2. Acid mucopolysaccharides in goblet cells and contents of crypts of the mucous membrane of a normal large intestine from a dog. Staining with Alcian blue, 15 ocular, 20 objective.

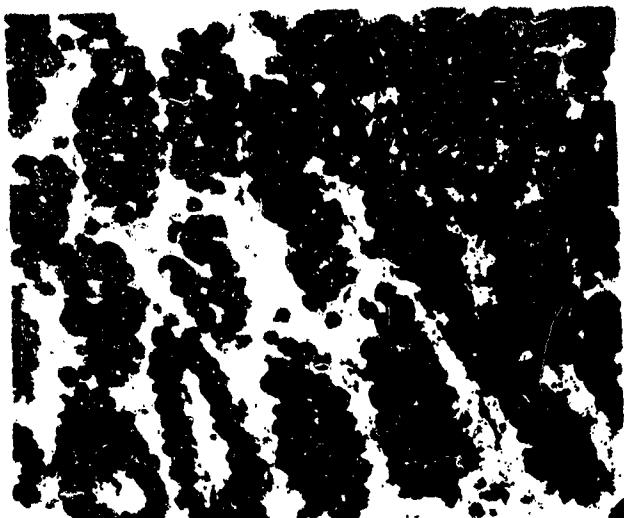


Figure 3. Acid mucopolysaccharides in goblet cells of mucous membrane of a large intestine transplant 20 days after plastic surgery. The number and size of the cells are increased. 15 ocular, 20 objective.



Figure 4. Sharply positive SHIK reaction in transitional epithelium of the urinary bladder 20 days after sigmoid cystoplasty. The SHIK-positive material is in the surface, interstitial, and basal zones of the transitional epithelium. 15 ocular, 20 objective.



Figure 5. Glycogen in the tunica muscularis of a large intestine transplant one month after operation. SHIK reaction. Microphoto. 10 ocular, 20 objective.

accompanied by a reinforcement of mucoid formation; together with reinforcement of glycogen breakdown, its surplus synthesis occurs here. According to the literature, [12, 15], and our data, these changes can be evaluated as a manifestation of a defense reaction of the bladder mucosa in response to the action of bacterial flora and products of secretion of the transplant mucosa. The development of lymphoid follicles in the submucosal layer is also connected with this reaction.

The question of the significance of the change in the quantity of glycogen in the musculature of the bladder is the basic form of deposition of carbohydrates in the musculature, in which process the amount of glycogen is a unique "passport" of metabolic reactions [16].

The decrease in the amount of glycogen in the tunica muscularis of the bladder after operation is connected with reinforcement of glycogenolysis. Such a nature of carbohydrate metabolism is evidently a manifestation of strengthened energy loss as a result of compensatory reinforcement of the work of the bladder stump. With the passage of time after the operation, the amount of glycogen is restored when the transplant is completely assimilated as an active component part of the urine reservoir. This can signify a restoration of normal metabolic processes in the muscle tissue of the bladder.

The content of glycogen is increased in the musculature of the transplants. In accordance with cystometric investiga-

tions by which reinforced contracting function of the walls of the transplants were observed, it can be thought that increased glycogen synthesis takes place here together with its increased loss. The accumulation of glycogen is most pronounced in the muscular coat of the small intestine segment during the first four months after operation (Figure 5); a slight increase in the amount of glycogen during 1-1½ months after operation is noted in the tunica muscularis of the small intestine segment.

Thus, new conditions lead to changes in processes of carbohydrate metabolism in muscles of the transplants. In this process, such changes are more pronounced in the musculature of the small intestine segment. The agreement of these data with the results of cystometric investigations compels us to suggest the presence of a connection between such changes in metabolism and the more pronounced "disorganizing" effect of contractions of the small intestine segment in comparison with large intestine transplants.

In the works of Sil'ven (see [17]), Kempani and Regianini [18], V. S. Peschanskiy, etc, the broad role of acid mucopolysaccharides in the process of regeneration is indicated. The process of development of scars in the area of bladder-intestine anastomosis after both kinds of plastic surgery is on the whole similar to the formation of any other scars: the proliferation of fibroblasts, the formation

and accumulation of amorphous substance containing acid mucopolysaccharides (chondroitin sulfate C, hyaluronic acid, and a small amount of chondroitin sulfate B) occurs earlier; collagenization of argentophilic fibers with a parallel diminution of the amount of acid mucopolysaccharides in the entire substance and an increase in the content of neutral mucopolysaccharides in the fibers occurs subsequently.

An inequality of scar formation processes is observed. Knitting of the walls of the intestine and bladder occurs earliest as a result of the development of connective tissue at the level of the connection of muscle and serous membranes, which agrees with the data of other authors ([2, 5], etc.). The slower development of a scar at the level of connection of the mucous membranes and also the submucosal layers is explained by the fact that these areas have undergone the action of the contents of the urine reservoir to a greater extent than others.

Toward the 20th day after the operation, the line of anastomosis is completely covered with epithelium; furthermore, transitional epithelium is being built up on the transplant mucosae. Epithelialization of the line of anastomosis primarily at the expense of transitional epithelium is explained by several factors: 1) the capacity of transitional epithelium as an epidermal type of tissue to build a multi-layered sheet on a wound surface under conditions of

regeneration ([15, 19], etc.); 2) the more rapid epithelialization of wounds of the urinary bladder in comparison with wounds of different parts of the digestive tract, as is seen upon comparison of data on regeneration of the intestine ([20, 21], etc.) and regeneration of transitional epithelium (see [15, 19]); 3) preservation of a more or less adequate medium for bladder epithelium, while the transplant is existing under entirely new conditions.

There is a relationship between epithelialization of the area of anastomosis and the degree of maturity of the underlying connective tissue. In accordance with data of N. N. Anichkov, K. G. Volkova, V. G. Garshin [22], G. D. Knyazeva [23], etc., it can be thought that young granulation tissue, rich in cells and mucoid substances and existing at the level of connection of the submucosal layers, creates conditions for accumulation and firm rooting of the epithelium. In its turn, the epithelial layer facilitates maturation of the underlying tissue.

We suggest that not only a reinforcement of glycogen breakdown, but also surplus synthesis, occur under conditions of regeneration in the epithelium of the urinary bladder as well as in other epithelia of the epidermal type. (see [24]). Reserves of nutrition for the accumulating cells are created, and the possibility of growth is ensured. The compact film distributed on the mucous membrane of the transplant plays the role of a foundation on which the transitional epithelium

can accumulate. This explains the presence of such epithelium on the villi close above (Figure 6).



Figure 6. Transitional epithelium, rich in glycogen, on the villi of the small intestine close above the line of anastomosis, one month after operation. SHIK-reaction. Microphoto. 15 ocular, 20 objective.

No discrepancies in the chemism of the fibers of the newly-formed connective tissue appear toward the 3rd month. However, proliferative inflammation occurs over a long period in the area where the silk fibers are located; here, acid mucopolysaccharides occur in a significant amount. Silk ligatures either move into the lumen of the urine reservoir as a result of the eliminative function of intestinal or

transitional epithelium, or are encapsulated; in the first case, they are the basis for the formation of calculi. The existence of foci of chronic inflammation and interlocking of epithelium can lead to a disturbance in scarification, and can be a cause of constriction of bladder-intestine anastomoses.

Processes of regeneration and the mucopolysaccharide dynamics connected with them occur monotypically; however, in colocystoplasty healing proceeds in the presence of large amounts of acid mucopolysaccharides; such substances are accumulated at the level of the connection of the submucosal layers earlier than in the case of ileocystoplasty, which is evaluated as a positive moment in healing. The process of scar formation at the level of connection of the tunica muscularis and tunica serosa occurs somewhat more rapidly after colocystoplasty.

CONCLUSIONS

1. In ileo- and sigmoidocystoplasty, monotypical changes in the course of certain histophysiological processes connected with mucopolysaccharide metabolism in the tissues of the transplants and the urinary bladder occur. These changes are complex adaptive reactions of the tissues to unusual conditions of functioning.

2. The nature and extent of such reactions, together with morphological details and cystometric data, make it possible for us to indicate advantages of sigmoid intestine in replacing part of the urinary bladder in comparison with

iliac intestine. The differences described, as well as the different cystometric characteristics, are conditioned by physiological peculiarities of small and large intestine.

3. In the process of healing, substantial growth of the walls of the bladder and transplant with complete epithelialization of the line of anastomosis, primarily at the expense of transitional epithelium, occurs.

4. Silk ligatures, passing into the lumen of the urine reservoir and disrupting the chemism of scar formation, can be a cause of calculus formation and one of the causes of stenosis of the bladder-intestine anastomosis.

5. Processes of healing of small intestine and large intestine-bladder anastomosis proceed monotypically. A certain retardation of scar formation processes in the case of ileocystoplasty is connected with the physiological characteristics of large intestine (living peristalsis, the content of strongly acting proteolytic enzymes in the intestinal fluid).

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